In general, the antileukotriene agents are very safe. Earlier agents that caused significant elevations of liver function tests are no longer manufactured, but some concerns regarding liver function remain. Zileuton ingestion has been associated with mild and transient elevation of liver enzymes that generally reverts to normal with continued therapy or cessation. The FDA has suggested that monitoring be done monthly for the first few months, and periodically thereafter. Churg-Strauss syndrome has been found in association with zafirlukast when corticosteroid anti-inflammatory therapy was being tapered. Thus asthma patients in whom corticosteroid therapy is being reduced should be carefully monitored. Adrenal suppression and cataracts have been mentioned as potential side effects; further study is required.

Antileukotrienes are currently recommended for mild persistent asthma by the National Heart, Lung and Blood Institute, and they may be effective in other subgroups of asthma.

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Combination Therapy for HIV Disease

As a result of recent advances, the treatment of HIV disease is now firmly based on HIV immunopathogenesis and viral dynamics. This paradigm shift—along with new, potent anti-retroviral drugs, a better understanding of drug resistance, and the ability to monitor viral load—has engendered updated recommendations for anti-retroviral therapy.

The concept of virologic latency after primary HIV infection is no longer tenable. HIV immunopathogenesis reveals that viral replication and clearance, as well as $CD4^+$ cell destruction and replacement, are rapid, continuous, high-level processes at all stages of the disease. Estimates suggest that 10 billion virions and 2 billion $CD4^+$ cells are produced and destroyed each day, and that the plasma virus half-life is only 6 hours. More than 99 percent of plasma viremia results from these ongoing cycles of infection in $CD4^+$ lymphocytes. Eventually, the immune system is overwhelmed by the unrelenting assault.

HIV infects multiple cellular compartments. Actively productive $CD4^+$ cells with short half-lives make up the first compartment, the major reservoir of virus in the body. A second compartment of longer-lived tissue macrophages and follicular dendritic cells accounts for 1% of the viral burden. A third compartment of chronically infected cells may exist (perhaps in the brain and cerebral spinal fluid), offering proviral DNA a long-term, possibly life-long, sanctuary site. The mathematical model for eradication of HIV suggests that complete viral suppression for a period of 2 to 3 years may eradicate the virus from the host in the first two compartments, but a risk of relapse remains from the sanctuary sites.

The ability to quantitate the level of HIV-1 RNA in the plasma (viral load) has been essential to our increased understanding of viral pathogenesis and anti-retroviral efficacy. Viral load is a practical and reliable marker of disease progression and treatment benefit.

Recent data has demonstrated a strong relationship between viral load and clinical outcomes. Natural history studies have demonstrated that baseline viral loads predict over a 10-year period of observation the rate of $CD4^+$ T-lymphocyte decline, the time to AIDS, and the time to death from AIDS. Similarly, clinical trials of nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors have consistently shown a strong correlation between reductions in viral load and reduced risk of $CD4^+$ T-cell decline, AIDS, or death from AIDS.

Within the past year, five new drugs have been approved for the treatment of HIV-1 infection: two nonnucleoside reverse transcriptase inhibitors (nevirapine and delavardine) and three protease inhibitors (ritonavir, indinavir, and nelfinavir). The addition of these agents has resulted in a growing number of potent virus-suppressing combination regimens. The term "highly active anti-retroviral therapy" (HAART) has been coined to describe these new, very effective, combinations.

The promise of these new combinations notwithstanding, it has become clear that the development of drug resistance remains the Achilles heel of anti-retroviral therapy. A new generation of HIV is produced in 2.6 days, yielding 140 generations per year. Assuming 10 billion replicative cycles per day, every possible mutation in the HIV genome can occur several times a day. Consequently, if HIV replication is not completely arrested, mutants will rapidly arise. Genotypic and phenotypic laboratory assays for drug resistance are in development.

Potent anti-retroviral combination regimens initiated in moderately advanced disease have demonstrated impressive immunologic, virologic, and clinical responses. The immunologic response is incomplete, however, with respect to full restoration of $CD4^+$ cell number and function, thus arguing in favor of earlier intervention.

The mantra of HIV therapy has become "hit early, hit hard." Significant scientific rationale exists for the new, more aggressive goal of suppressing HIV replication as completely as possible throughout the entire course of infection. Powerful, theoretical rationale exists as well for intervening as early as possible in the course of HIV disease to avoid irreversible immune deficits. Highly

effective combination anti-retroviral therapy is the new standard of care.

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Advances in Allergic Rhinitis Pharmacotherapy

A recent survey shows the prevalence of allergic rhinitis to be at least 14% in the US population. Therapeutic options for allergic rhinitis are threefold: pharmacotherapy, immunotherapy, and environmental control. Pharmacotherapy has provided the major advances over the last 10 years with regard to improved efficacy and safety in the treatment of this disease.

Five agents are now available in the category of oral second-generation antihistamines: terfenadine, astemizole, loratadine, cetirizine, and fexofenadine. These histamine receptor antagonists are less sedating than their first-generation predecessors, and thus are well tolerated by patients. Terfenadine and astemizole, however, can cause QT prolongation and, in rare cases, a serious and potentially fatal cardiac arrhythmia. The Food and Drug Administration has therefore recommended removal of terfenadine from the market. The other three agents do not appear to have this property. Advantages of the second-generation antihistamines include a complete lack of somnolence and mental impairment (astemizole, loratadine, fexofenadine), the convenience of once-a-day (astemizole, loratadine, cetirizine) or twice-a-day (terfenadine, fexofenadine) dosing, and, consequently, improved patient acceptance and compliance. Liquid preparations and pediatric indications (age 6 years and up) now exist for loratadine and cetirizine. Certain antihistamine-decongestant combination agents are on the market, although patients who use them need to be warned about potential stimulatory side effects from the decongestant. Second-generation antihistamines have also recently become available for topical use. Azelastine hydrochloride, a moderately effective intranasal spray, is particularly useful in decreasing nasal itching; mild sedation occasionally occurs due to its systemic absorption via the nasal mucosa.

The well-proven potency, efficacy, and safety of intranasal corticosteroids have made them the drugs of choice for any patient with frequent, chronic, or severe symptoms of allergic rhinitis. A number of topical agents are available (beclomethasone diproprionate, budesonide, flunisolide, fluticasone, triamcinolone, dexamethasone). Comparison studies evaluating topical steroids versus oral antihistamines repeatedly show intranasal corticosteroids to be superior. Unlike all other pharmacotherapy agents, when used alone, intranasal corticosteroids can improve all four of the major symptoms of allergic rhinitis (itch, rhinorrhea, sneeze, and congestion). Their use has increased for a variety of reasons, including a better understanding of the inflammatory nature of allergic rhinitis and the decision to introduce them earlier and maintain them longer when allergen exposure or symptoms continue. They are available as either a wet aqueous spray or a dry aerosol spray, making them convenient and well accepted by most patients. Differences in clinical efficacy between agents is minimal, so selection of a specific nasal steroid usually depends on cost, formulary availability, and patient preference (aqueous or aerosol). At recommended doses, intranasal corticosteroids are free of significant adverse effects.

Another topically active anti-inflammatory agent, cromolyn, has been found to be so safe after years of use that it was recently made available without a prescription. Cromolyn is an nonsteroidal nasal spray whose mode of action is primarily preventive via mast cell stabilization and, overall, less effective than nasal corticosteroids.

Oral anticholinergic therapy has been tried for years as therapy for allergic rhinitis, but adverse effects (such as dry mouth and eyes) have limited its use. A topical anticholinergic medication has recently become available that circumvents the side effects of the oral form: ipratroprium bromide. This nasal spray, available in two strengths (0.03 and 0.06%), appears to be an effective adjunct in controlling rhinorrhea.

New agents and approaches hold additional promise for the treatment of allergic rhinitis. The leukotriene receptor and pathway antagonists, available for asthma, are being tested as therapeutic agents in oral and topical forms. Monoclonal antibodies to IgE and to cytokines important in allergic inflammation are still in early experimental stages but will likely be tried as therapy for this disease.

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